(11) 1358915

PATENT SPECIFICATION

1358915

(21) Application No. 42625/71 (22) Filed 13 Sept. 1971
(44) Complete Specification published 3 July 1974
(51) International Classification A61J 3/06 A61K 9/00
(52) Index at acceptance
B5A 1R9
A5B 730 731 733 734 73Y 750 751 75Y 764

(72) Inventors LEWIS DAVID MORSE and PAUL ALOYSIUS HAMMES

(19)

(54) DIRECTLY COMPRESSED TABLET AND COMPOSITION THEREFOR

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to edible tablets, particularly pharmaceutical tablets containing biologically active agents such as vitamins, minerals, nutrients or drugs or their mixture.

Almost all biologically active agents of crystalline or powdered material have to be put through either a so-called dry granulation series of steps or a wet-granulation series of steps to obtain a composition that can be compressed into satisfactory tablets. A simple mixture of the active agents with the usual pharmaceutical binders, diluents and lubricants can be compressed directly into a tablet but they may not possess the desired strength and resistance to shock. To obtain a satisfactory tablet the tablet forming composition has required a preliminary formation into granules of predetermined size.

The dry granulation process requires that the tablet forming mixture first be compressed into large hard slugs under high pressures. Those slugs are then reduced to a granular size which can then be recompressed to a finished tablet in a conventional tablet compression machine. This granulation operation is costly because it requires expensive machines, working space and labor and because the several steps involve a considerable time.

The wet granulation process similarly has its drawbacks. It first involves mixing the tablet ingredients and then their wetting with a liquid such as water, alcohol or other organic solvent. This properly wetted preparation is then dried in an oven and the solid compacted mass is reduced into granules f the proper size for tableting in a tablet compression machine. This entire process, like the dry granulation process, requires high priced apparatus, liquids that may be expensive, skilled workmen and considerable time, all of which adds to the high cost of the tablets.

In accordance with the present invention, tablets containing a biologically active agent are made by encapsulating particles of the said agent with a coating material permeable to stomach or intestinal fluids and having chemical groups that are subject to intermolecular bonding forces, and compacting a body of the encapsulated particles into a tablet without a preliminary granulation process.

The present invention by-passes all of the intermediate steps of the wet and dry granulation processes as the tableting mixture is directly supplied to the tableting machine and tablets are obtained; hence, this is referred to as a direct compression process, which term is to be understood as meaning that the granulation steps are omitted and the tableting mixture is directly supplied to the tableting machine. The invention is based on the discovery that this direct compression process is made possible if the active agent has been microencapsulated in a coating material in accordance with known techniques.

Although the technical reason for the direct compressibility feature of microencapsulated agents is not fully understood a possible explanation is that the coating materials are all subject to intermolecular bonding forces. These forces arise from groups such as hydroxyl, carboxyl and amino in the chemical compounds of the coating materials. The compaction of the materials in the tableting machine apparently causes these intermolecular bonding forces to exert their cohering effect and bind the tablet together.

This invention contemplates the use of any microencapsulated solid biologically active agent to make tablets by direct compression. These agents include vitamins, powdered iron

and its biologically available salts, biologically available calcium, sodium, and potassium salts, amin acids, steroids, enzymes and compounds which are therapeutically active as hormones, antibiotics, analgesics, antihistamines, diuretics, mental depressants and anti-depressants, hypertensives, hypotensives, blood anticoagulants, germicides, fungicides, anthelmintics, obesity reducers, antigens and antacids.

The tablets made by directly compressing the microencapsulated drug, which constitute another embodiment of the present invention, have the added feature that they have high mechanical strength, resist fracture, and have an attractive glossy surface. Despite these desirable properties they can release the active agent readily into the gastro-intestinal tract, because the wall of the microencapsulating material is permeable to stomach or intestinal fluids, which diffuse into the capsule and leach the internal phase from the capsule so that it is biologically available.

The microencapsulation of the active agent may involve the known arts of polymer/polymer incompatibility coacervation, and film formation from polymer solution by loss of solvent. Representative of this prior art are British patent 1,016,839 and U.S. patents 3,155,590, 3,495,988 and 2,800,457. Other microencapsulation processes which may be used are disclosed in Netherlands patent 6,611,661 and in French patent 1,453,745.

If the agent to be encapsulated is water-soluble such as potassium penicillin, the microencapsulation process, which is discussed below should not use water. One good coating for this purpose is ethylcellulose, which is water-insoluble; a suitable solvent is cyclohexane. The ethylcellulose should preferably have a 47.5% ethoxyl content and a 100 cps. viscosity but a range of 45 to 50% ethoxyl content and a 95—110 cps. viscosity is permissible. The viscosity is measured by known methods, at 25° as a 5% by weight solution in an 80:20 toluene-ethanol mixture. On the basis of 100 grams of cyclohexane there can be added 1 to 5 grams of the ethylcellulose, thereby varying the wall thickness which controls the release time of the water-soluble agent. A preferred amount of ethylcellulose is 2 grams. Other suitable coating materials are hydroxypropylmethyl cellulose, hydroxyethyl cellulose, ethylhydroxyethyl cellulose and hydroxypropyl cellulose.

The phase separation inducing agent is polyethylene and the material which is preferably used should have a molecular weight of between 5000 to 10,000 (an average of 7000 is preferred) and from 1 to 5 grams of it should be added per 100 grams of the cyclohexane, and preferably 2 grams. The present invention, however, involves the elimination of a phase-separation-inducing agent and the use only of the coating agent in the solvent.

If the drug to be encapsulated is not soluble in water, an aqueous system for microencapsulation may be used. For instance, indomethancin may be microencapsulated in a gelatin-gum arabic water system, e.g. using the techniques of the U.S. patent 3,495,988.

The agents to be coated preferably are of a particle size to pass through a U.S. No. 100 gauge sieve but this is by no means essential as the particles may range from as large as a 20 gauge down to as small as to pass through a 320 gauge sieve. The amount may vary over a wide range, namely from 2 to 120 grams based on 100 grams of the liquid phase.

The following examples, in which capsule sizes are U.S. standards are illustrative of the invention:

EXAMPLE 1

The following were dispersed in 1500 gm. cyclohexane, using an upthrust turbine impellor:

30 gm. Ethylcellulose (47.5% ethoxyl content by weight; viscosity 100 cps. as 5% solution in 80:20 toluene:ethanol at 25°C).
30 gm. Polyethylene granules (molecular weight about 7000).
550 gm. Sodium Ascorbate (88%>60 mesh<140 mesh).

The mixture was stirred with heating; at 80°C. both the ethyl cellulose and the polyethylene had dissolved in the cyclohexane.

Stirring was continued while the system was allowed to cool. As the temperature dropped, solvated ethylcellulose developed as a separate phase due to the presence of the polyethylene. This is a known art, described in the literature as an example of coacervation resulting from polymer/polymer incompatibility. The solvated polyethylene, distributed in the cyclohexane as droplets by the turbine, tended to wet the sodium ascorbate particles and to envelop them. As the temperature dropped further, the ethylcellulose lost solvent and developed into solid encapsulating walls. The continuous phase, cyclohexane, contained minute particles of polyethylene. At 35°C the walls had stopped building up. Cold cyclohexane was added to reduce the temperature still further. The supernatant cyclohexane was poured off together with the minute particles of polyethylene. The microcapsules were resuspended in clean cyclohexane. This was continued until the capsules were washed clean of polyethylene and other debris. The capsules were spread to dry. The resultant capsules, with 95% sodium ascorbate content, when

screened through standard Taylor sieves, had the following size distribution (wt.%):

−16/+20	0.2
−20/+30	19.8
−30/+40	37.3
−40/+60	33.5
−68/+80	7.5
−80/+100	1.4
−100/+140	0.1

Laboratory personnel found no salty or sour taste when they put several capsules on the tongue and swallowed them.

Microcapsules dispersed in simulated gastric fluid at 37°C released their content in less than five minutes.

500 gm. of these microcapsules were blended with 0.5% magnesium stearate (lubricant). The blend was compressed in a conventional tableting machine, run at 100 tablets/minute using a No. 1 capsule shaped punch.

The resultant tablets averaged 625 mg. each and had a thickness of 0.225". They had a very good whiteness. Flow from the hopper to the punch of the tableting machine was far superior to unencapsulated material. Strong-Cobb hardness of the tablets (see "Theory & Practice of Industrial Pharmacy" by L Lachmann et al, Lea & Febeger (1970) was 21.9 kg. With granulated sodium ascorbate about 18 kg would be expected.

EXAMPLE 2

Capsules were prepared successfully, as in Example 1, but this was a scaled-up batch employing the following quantities of materials:

8 liters cyclohexane
120 grams ethylcellulose
120 grams polyethylene
2200 grams sodium ascorbate

The microencapsulated product has the following Taylor sieve analysis (wt. %):

+12 mesh	1.2
−16/+20	3.1
−20/+40	2.5
−40/+60	25.8
−60/+80	38.4
−80/+100	18.4
−100/+140	3.4
−140/+200	5.1
−200/+325	0.1

These microencapsules were compressed into tablets as explained in Example 1.

EXAMPLE 3

Capsules were prepared successfully, as in Examples 1 and 2, but this was a scaled-up batch employing the following quantities of materials:

70 gallons cyclohexane
851 grams ethylcellulose
851 grams polyethylene
15.6 kilograms sodium ascorbate

The Taylor sieve analysis (wt. %) of the encapsulated product is as follows:

+12 mesh	2.0
−12/+16	5.5
−16/+20	5.6
−20/+30	6.4
−30/+40	6.5
−40/+60	22.3
−60/+80	29.9
−80/+100	14.3
−100/+140	5.3
−140/+200	1.1
−200/+325	0.5
−325	0.6

500 gm. of these microcapsules were tableted as in Example 1. The resultant tablets had a Strong-Cobb hardness of 19.9 kg. Another 500 gm. of the microcapsules of Example 3 were tableted as in Example 1, but without including the lubricant magnesium stearate. The resultant tablets had a hardness of 22.0. The fact that no lubricant or filler or other pharmaceutical excipient is required is important because a smaller tablet can be made or, from a different viewpoint, space is provided for the presence of other medicinal agents in the same size tablet. In either event, a strong tablet is produced.

EXAMPLE 4

Other examples of the invention are obvious from a consideration of the relative amounts of the ingredients, provided that they specifically fall within the range set forth in the general description of this invention. These additional examples could substitute ethylcelluloses having a different ethoxyl content and a different viscosity within the ranges set forth. Alternatively, the molecular weight of the polyethylene may be varied within the range set forth instead of that specified in the examples. In like manner the amount of each ingredient used in making a batch can vary within the ranges defined for each, instead of the precise amount in the examples.

EXAMPLE 5

This example shows that a gelatin/gum Arabic encapsulating agent gives directly compressible material in accordance with the present invention.

An 11% solution f 250 Bloom porkskin gelatin in distilled water was prepared (I)

and held at 55 C. An 11% solution of gum Arabic in distilled water was prepared (II) and held at 55°C.

90 Ml. of (I), 90 ml. of (II) and 350 ml. distilled water (previously warmed to 55°C) were blended and kept stirring with a flat bladed impeller. Microscopic examination of this blend (III) showed an essentially clear liquid. The pH of III was adjusted to 4.5 with 10% aqueous acetic acid. Microscopic examination now showed a rich dispersion of the highly hydrated protein-gum complex was kept stirring, and allowed to cool to 40°C. At that temperature 54 gm. indomethacin was added. The system was allowed to cool slowly. At 38°C microscopic examination showed that coacervate droplets were wetting small aggregates of indomethacin particles. The coacervate droplets fused together to form a hydrated film. As the temperature dropped to 25°C., wall build-up continued. At 25°C there were discrete microcapsules of aggregated indomethacin particles. The system was chilled to 10°C and 4.5 ml. of 25% aqueous glutaraldehyde was added to crosslink the capsular wall material. The system was allowed to stir overnight. The capsules were washed with chilled, distilled water and air dried.

The resultant capsules were frangible clumps containing 75% indomethacin. They released indomethacin gradually in simulated gastric fluid.

The microcapsules were compressed in a conventional tableting machine, using a No. 1 capsule shaped punch.

The resultant tablets averages 383 mg. each and had a thickness of 0.196" Strong-Cobb hardness of the tablets was higher than 27.3 kg. (as high as our equipment measures.)

EXAMPLE 6

An 11% solution of 250 Bloom porkskin gelatin in distilled water was prepared (I) and held at 55°C. An 11% solution of gum Arabic in distilled water was prepared (II) and held at 55°C. A 2% solution of ethylene maleic anhydride copolymer (Visc. 2.0 cps. before pH adjustment), adjusted with sodium hydroxide to pH 9 was prepared (III). A 2% solution of ethylene maleic anhydride copolymer (Visc. 7.0 cps before pH adjustment) adjusted with sodium hydroxide to pH 9 was prepared (IV).

90 ml. of (I), 90 ml. of (II), 20 ml. each of (III) and (IV), were blended with 500 ml. distilled water (Previ usly warmed to 55°C), and kept stirring with an upthrust turbine impellor. The pH of the system was 7.0. Microscopic examination showed a rich dispersion of coacervate droplets of gelatin/gum Arabic/ethylene maleic anhydride copolymer in water. The dispersion of the highly hydrated colloidal complex was kept stirring and allowed to cool to 35°C. At that temperature 72 gm. ferrous fumarate was added. Microscopic examination showed that coacervate droplets were wetting small aggregates of ferrous fumarate was added. Microscopic examination showed that coacervate droplets were wetting small aggregates of ferrous fumarate particles. The coacervate droplets fused together to form a hydrated film. As the temperature dropped to 25°C, wall build-up continued. At 25°C there were discrete microcapsules of aggregated ferrous fumarate particles. The system was chilled to 10°C. Some of the slurry (V) was removed for later treatment. To the rest of the slurry (VI), 430 ml., was added 2.0 ml. of 25% aqueous glutaraldehyde to crosslink the capsular wall material. System (VI) was allowed to stir overnight. Capsules of slurry (V) and (VI) were washed with chilled distilled water, dehydrated by washing with anhydrous ethanol, and then air dried.

The crosslinked capsules, screened through Taylor sieves, had the following size distribution:

	% by weight
+60 mesh	0.6
−60/+100	1.5
−100/+200	40.4
−200/+270	41.9
−270/+325	8.2
−325	7.3

0.25 gm. of the −325 mesh fraction was dispersed in 200 ml. simulated gastric fluid at 37°C in a shaking, temperature controlled. All of the iron was released in five minutes.

The microcapsules of the −200/+270 fractions were compressed as in Example 1. The resultant tablets averaged 745 mg. each and had a thickness of 0.221". Strong-Cobb hardness of the tablets were higher than 27.3 kg.

EXAMPLE 7

Capsules were prepared successfully as in Example 1 but no polyethylene was used.

The resultant capsules were directly compressible with a Strong-Cobb hardness of greater than 27.3 kg.

EXAMPLE 8

Capsules were prepared successfully as in Example 7, but the ethylcellulose used had a viscostiy of 45 cps. rather than 100 cps.

The resultant capsules were directly compressible with a Strong-Cobb hardness of 25.5 kg.

EXAMPLE 9

To 400 gm. 1% aqueous hydroxypropyl methylcellulose was added 50 gm. finely divided reduced iron (metallic iron), with

stirring. 400 ml. 25% dextran solution was added slowly with stirring. This phased out the hydroxypropyl methylcellulose. The system was heated at 60°C for 1/2 hour to harden the capsule walls. 7.5 gm. 25% aqueous tannic acid was added to crosslink the capsule walls and thereby strengthen them. The system was stirred for 2 hours. The capsules were washed with cold water and spread to dry.

The resultant microcapsules were directly compressible as in Example 1.

EXAMPLE 10

30 gm. finely divided reduced iron (metallic iron) is dispersed in 700 gm. 10% aqueous hydroxyethylcellulose (300 cps. at 20°C. as a 5% aqueous solution). The dispersion was spray dried at 245°F to yield microcapsules that were directly compressible as in Example 1.

EXAMPLE 11

A 36% aqueous solution of gelatin was brought to 40°C with stirring. 50 gm. Riboflavin Superfine Powder (Merck Type 59921) was added with stirring, keeping the temperature of the system at 40°C. to form System I.

System I was added with stirring to 600 gm. white mineral oil. The white mineral oil was at 30°C. The resultant System II was a slurry of gel in mineral oil, the gel entraining riboflavin. The slurry particle size was about 100 μ.

System II was poured with stirring into 3 liters 95% ethanol previously adjusted to 20°C. The System III was allowed to stir for an hour to allow dehydration of the spheres. Liquid was decanted. The spheres were washed with 95% aqueous ethanol at 20°C and spread to dry.

The resultant product was directly compressible as in Example 1.

EXAMPLE 12

33.3 Gm. finely divided reduced iron was added with stirring to 200 gm. 50% aqueous gum Arabic at 10°C to yield System I.

System I was added to a mixture of 500 gm. castor oil and 250 gm. ethanol at 10°C, with stirring to yield a slurry of 100 μ spheres in the liquid, constituting System II.

System II was added to 2 liters anhydrous ethanol at 10°C. with stirring. Stirring was continued to allow for dehydration of the spheres.

The spheres were drained of liquid, washed with ethanol and spread to dry.

The resultant product was directly compressible as in Example 1.

EXAMPLE 13

Spheres were prepared as in Example 12, using however, 25% aqueous poly (methyl vinyl ether) maleic anhydride, specific viscosity 0.1—0.5) in place of the 50% aqueous gum Arabic. The resultant spheres were directly compressible as in Example 1.

EXAMPLE 14

Spheres were prepared as in Example 12, but using gum carrageenan in place of the gum Arabic. The resultant spheres were directly compressible as in Example 1.

EXAMPLE 15

Spheres were prepared as in Example 12, using polyethylene maleic anhydride (low molecular weight) in place of the gum Arabic. The resultant spheres were directly compressible as in Example 1.

EXAMPLE 16

Example 12 was carried out with Algin in place of gum Arabic.

EXAMPLE 17

Example 12 was carried out with gum Guar in place of gum Arabic.

EXAMPLE 18

Example 12 was carried out with locust bean gum in place of gum Arabic.

EXAMPLE 19

Example 12 was carried out with yellow dextrin in place of gum Arabic.

EXAMPLE 20

Example 12 was carried out with British gum in place of gum Arabic.

EXAMPLE 21

Example 12 was carried out with poly (acrylic acid) in place of gum Arabic.

EXAMPLE 22

The following were dispersed in 300 gm. cyclohexane, using an upthrust turbine impeller:

6 gm. ethylcellulose (47.5% ethoxyl content by weight; viscosity 100 cps. as measured above).

6 gm. polyethylene granules (molecular weight about 7000).

110 gm. thiamine mononitrate, sized to pass through a 320 gauge sieve.

The system was stirred with heating. At 80°C. both the ethylcellulose and the polyethylene had dissolved in the cyclohexane.

Stirring was continued while the system was allowed to cool. As the temperature dropped, solvated ethylcellulose developed as a separate phase due to the presence of the polyethylene. This is a known art, described in the literature as an example of coacerva-

tion resulting fr m polymer/polymer incompatibility. The solvated polyethylene, distributed in the cyclohexane as droplets by the turbine, tended to wet the thiamine mononitrate particles and to envelope them. As the temperature dropped further, the ethylcellulose lost solvent and developed into solid encapsulating walls. The continuous phase, cyclohexane, contained minute particles of polyethylene. At 45°C the walls had stopped building up. Cold cyclohexane was added to reduce the temperature still further. The supernatant cyclohexane was poured off together with the minute particles of polyethylene. The microcapsules were resuspended in clean cyclohexane. This was continued until the capsules were washed clean of polyethylene and other debris. The capsules were spread to dry.

The resultant capsules, with the theoretical 94.7% vitamin content, when screened through standard Taylor sieves, were 7.4%+60 mesh, and 92.6%−60 mesh. Laboratory personnel found no bitter taste when they put several capsules on the tongue and swallowed them.

To demonstrate nutritional availability of the vitamin, 0.50 gm. capsules were put into 200 ml. simulated gastric fluid at 98.7°C. and held in a shaking temperature controlled water bath. All of the internal phase was found to have been released from the capsules in five minutes.

EXAMPLE 23

The process of Example 22 is carried out using ethylcellulose within the range of 3 to 15 grams.

EXAMPLE 24

Capsules were prepared successfully, as in Example 22, but only 3 gm. polyethylene granules were used. This was sufficient to phase out the ethylcellulose. Also, only 45 gm. thiamine mononitrate was used. This provided thicker capsule walls, with a theoretical vitamin content of only 88.2%.

EXAMPLE 25

Capsules were prepared successfully as in Example 24, but thiamine hydrochloride was the encapsulated material.

EXAMPLE 26

Capsules were prepared successfully as in Example 25, but 6 gm, thiamine hydrochloride was used. This provided very thick capsule walls, with a theoretical vitamin content of only 50%.

EXAMPLE 27

The processes of Examples 22 to 26 are carried out but the thiamine compound is mostly of larger 20 gauge sieve size. Any in between size may be used and a 100 gauge size is preferred.

The capsules of Examples 22 to 27 are fed into a press as in Example 1 and the tablets are directly c mpressed into hard tablets which resist fracture but which yield their internal phase agent upon oral consumption.

Medicaments that may be microencapsulated and then be directly compressed into tablets include adrenergic agents such as ephedrine, desoxyephedrine, phenylephrine and epinephrine, cholinergic agents such as physostigmine and neostigmine, antispasmodic agents such as atropine, methantheline and papaverine, curariform agents such as chlorisondamine, tranquillizers and muscle relaxants such as fluphenazine, chlorpromazine, trifluprom azine, mephenesin and meprobamate, antihistamines such as diphenhydramine, dimenhydrinate, tripelennamine, perphenazine, chlorprophenazine and chlorprophenpyridamine, hypotensive agents such as rauwolfia and reserpine, cardioactive agents such as benzylhydroflumethiazide, flumethiazide, chlorothiazide, and aminotrate, steroids such as testosterone, fludrocortisone, triamcinolone, cortisone and prednisolone, antibacterial agents, e.g. sulfonamides such as sulfadiazine, sulfamerazine and sulfisoxazole, antimalarials such as chloroquine and antibiotics such as the tetracyclines, nystatin, streptomycin, penicillin, grisofulvin, sedatives such as chloral hydrate, phenobarbital and other barbiturates, glutethimide, antitubercular agents such as isoniazid, analgesics such as aspirin and meperidine, insulin and other polypeptides, vitamins, enzymes and blood products.

It has been stated above that the microcapsules containing the active agent may be directly compressed and this is illustrated in Example 5 as no other ingredient is present. This produces a tablet having a maximum hardness. The invention contemplates the addition of other ingredients such as the lubricant in Example 1, and other pharmaceutical excipients such as fillers like talc and flavoring or coloring agents. Moreover, the invention includes the combination with the microencapsulated agent of a non-coated biologically active agent and the direct compression of the mixture into tablets. The presence of these added uncoated ingredients or agents will tend to reduce the hardness of the tablet and consequently the amount of such added material is a self-limiting factor to still obtain a tablet of the desired hardness.

For instance, to the microencapsulated riboflavin of Example 11 may be added non-coated thiamine in the relative amounts in conventional capsules and this mixture can be directly compressed. Or, to the microencapsulated thiamine mononitrate of Example 22 may be added non-coated riboflavin in the appropriate mixture and this is to be directly

compressed. An added feature f such mixtures is that they flow freely in the tableting machine.

WHAT WE CLAIM IS:—

1. A method of making tablets containing a biologically active agent, that comprises encapsulating particles of the said agent with a coating material permeable to stomach or intestinal fluids and having chemical groups that are subject to intermolecular bonding forces, and compacting a body of the encapsulated particles into a tablet without a preliminary granulation process.

2. A method according to claim 1 in which the chemical groups are hydroxyl groups.

3. A method according to claim 1 in which the chemical groups are carboxyl groups.

4. A method according to any one of claims 1 to 3 in which the agent is a nutrient.

5. A method according to any one of claims 1 to 3 in which the agent is a drug.

6. A directly compressed tablet (as herein defined) containing an aggregation of biologically active agent particles that are encapsulated in a coating material permeable to stomach or intestinal fluids and having chemical groups subject to intermolecular bonding forces and that have been compacted into a tablet by direct compression as herein defined.

7. A tablet according to claim 6 in which the chemical groups are hydroxyl groups.

8. A tablet according to claim 6 in which the chemical groups are carboxyl groups.

9. A tablet according to any one of claims 6 to 8 in which the agent is a nutrient.

10. A tablet according to any one of claims 6 to 8 in which the agent is a drug.

11. A tablet according to any one of claims 6 to 10 that includes more than one biologically active agent.

12. A method according to claim 1 substantially as hereinbefore described in any one of the foregoing Examples.

13. A tablet according to claim 6, when prepared by a method according to any one of claims 1—5 and 12.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 and 10 Staple Inn,
London, WC1V 7RD.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.